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COMPLETE SPECIFICATION.

"A process for producing carriers for medicinal substances."

I, ISRAEL LIPOWSKI, of Hotel Regina, Quai du Mont-Blanc, Geneva, Switzerland, of Peruvian nationality, Physician, hereby declare this invention and the manner in which it is to be performed, to be fully described and ascertained in and by the following statement:—

The present invention relates to a process for producing a coating for medicinal substances in which the medicinal substances are reduced to the form of small bodies and the plurality of bodies thus obtained are coated over in groups with various membranes and the resulting groups, each consisting of approximately the same number of bodies, are mixed together.

It is already known that certain medicinal substances are rapidly and almost simultaneously dissolved and absorbed in the upper part of the small intestine although they were made in the form of small bodies such as very small pills, and the like and were coated with one or more protecting layers of varying thickness to prevent solution in the gastric juice. This process has several disadvantages. The medicinal substance acts suddenly and with full effect on a prescribed portion of the intestinal tract thus frequently giving rise to local injury of the intestinal mucous membrane and if the absorption of the substance is too rapid more or less severe poisoning effects may occur. Since the action of certain medicines depends upon a slow but constant supply thereof to the organ, in many cases the optimum effect could not be obtained by using carriers of the known types.

According to the present invention the carrier for the medicinal substances consists of about ten groups of pills, tablets, granules and the like divided as small as possible, the first group of which is covered with one, the second with two, the third with three coats and each successive group is provided with one protecting layer more than the last one. These ten groups, each containing a similar number of bodies, are uniformly mixed together.

Preferably the individual protecting coatings are exceptionally thin so that for example about ten coats together are scarcely more than about 1/10 mm. The material and nature of the coatings must be such that the bodies of the individual groups only dissolve in the stomach or intestine after various specified periods according to the number, material and nature of the coatings owing to their destruction by the gastric juices. It is not necessary for the coatings to consist of one and the same material and preferably the individual bodies may be provided with coatings of various materials.

In some cases the destruction of the coatings may be effected by actual solution in the stomach or intestinal juices but generally it is advisable to use materials [illegible]

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the coatings which are permeable or preferably semi-permeable to the stomach or intestinal juices, so that owing to osmotic processes the juices penetrate into the bodies which causes the bodies to swell and burst the coating or coatings, thus liberating the contents. As processes of this nature take place in almost all biological fluids they are as good as independent of the particular state of the stomach and intestinal mucous membrane.

The extent of the resistance of the coatings against destruction by the biological aqueous liquids may be affected by various circumstances such as for example the choice of the coating material and the material added thereto, the concentration of the solution used for the coating material, the number of superimposed coatings and the selection or sequence of the coatings consisting of various materials.

Coatings of rubber are particularly suitable because they are soft and highly elastic, next come coatings of cellulose esters, cellulose ethers, and the like such as for example nitro, acetyl, ethyl or benzyl cellulose. All these substances may be made elastic and pliable by adding softeners such as fats or wax or higher hydrocarbons such as paraffin, and the like. By adding resins such as Dammar, Sandarac, benzoin resin, mastic, shellac, colophony or tolu balsam to collodion solution or by using mixtures of such substances the resistance of the coatings can be strengthened. Furthermore by adding gluten or keratin as a constituent of various kinds of lacquers a desired resistance of the coating may be produced. Single coatings may consist of resins or mixtures of resins alone.

When applying various coatings to one and the same body between two layers of any particular material a packing layer of softer material consisting of fat for instance may be provided whereby numerous graduated effects can be obtained. The said packing layers may consist of cocoa butter, stearic acid and solid paraffin.

The coating materials may be used in solution like solutions of rubber in benzene for example, solutions of suitable cellulose derivatives in appropriate solvents and also as suspensions such as gluten or keratin in suitable lacquers.

According to the selection of the materials or other conditions for the production of coatings, ordinary coatings or compositions coatings may be produced on bodies of medicinal substances which remain undisturbed in the biological fluids for 10 minutes or 3 to 6 hours or up to 20 hours. In every instance the materials for the coverings may be selected so that all detrimental effects of the drugs are avoided. Keratin coverings can be produced which do not adversely affect the drug or the coating vessel.

When it is necessary to make the carrier or individual groups thereof insoluble in the stomach, the last coating may contain keratin or gluten, and the like. As almost all the coatings of medicinal carriers do not dissolve but are ruptured owing to increasing internal osmotic pressure, this process is almost completely independent of the fluids surrounding the carrier. Accordingly the resistance of the coatings is the same in the stomach and intestinal juices as in ordinary water. If coatings of this nature are applied so that they can withstand aqueous solutions for 3 to 4 hours then these coatings form a complete substitute for keratin and gluten coatings. This fact, however, does not preclude the occasional use of keratin and gluten.

Experience has often shown that a single or a number of applied layers are still too permeable which is sometimes a serious disadvantage because certain easily diffusing substances are osmotically balanced too easily. There are two methods of reducing the permeability of the coatings, viz by mixing wax with the material used for the coating and the introduction of a very thin layer of talcum between individual coatings. Wax however may only be used in conjunction with other suitable media because rubber or collodion for example are usually partly split in their solutions by wax. A solution of wax in a mixture of benzene and xylol is most suitable. These two solvents are the gentlest of all and they may be safely added to almost all other solvents. The addition of talcum must be effected with extreme care so that no clogging of the coating occurs thus undesirably reducing permeability.

With drugs which are insoluble or difficult to dissolve rupturing of the coatings owing to the bodies swelling is either quite impossible or at least becomes very difficult because insufficient solvent for the drug is formed inside the coating. In such cases

a more or less thick layer of a water soluble or water swelling material such as a layer of sugar is applied on the bodies before applying the first semi-permeable coating. When drug carriers treated in this manner come into contact with aqueous liquids water diffuses through the coating and together with the sugar or the like forms a solution which becomes increasingly diluted which eventually ruptures the membrane or membranes applied thereon. From this it may be seen that by selecting the water soluble or water swelling material and by making the layer produced therefrom of suitable thickness so that the stability of the drug carrier against the action of biological fluids can be controlled within wide limits, also the degree of the water solubility of the drug itself or its ability to swell in water can be taken into account.

According to the invention the appropriate doses of the drug consist of a plurality of very small bodies such as small pellets of about 1 to 2 mm. in diameter. These pellets consist of about 10 groups which only differ from one another in that each successive group has one coating more than the next one, i.e. if a teaspoonful of the dose consists of 50 pellets then 5 of these pellets have one coating, another 5 have two coatings the next 5 three coatings and the like so that the last group has ten coatings. This quantity of pellets is taken as one dose. The pellets which have only one coating are dissolved in the upper portion of the intestine, those with two coatings dissolve in the successive portion, and the like so that the pellets with ten coatings are only dissolved and absorbed when they reach one of the last portions of the intestine in which absorption can take place. The effect of this is that from the commencement of absorption in the first portion of the intestine until absorption is completed in the last part of the intestine, a definite period of from 6 to 10 hours elapses which is determined by the resistance of the various coatings. In this manner a constant supply of the bodies containing the appropriate drug in relatively small non-irritant doses is assured.

On account of the exceptionally thin nature of the pills the coating vessel cannot always be used in which case the pills may be moistened with the substance solution from which the coatings are formed in sufficiently wide glass vessels by careful shaking and rotary movements and then be placed on a smooth metal sieve where the solution is quickly evaporated and the coatings become uniform by the rotary movement of the sieve or the materials in solution for forming the coatings are sprayed or vaporised on or applied in any other finely divided manner on the pills, tablets, and the like from suitable slowly rotating tanks.

Preferably the keratin or gluten coatings are not produced according to the hitherto known methods in which a solution of the keratin in acetic acid and the like was necessary which was liable to injure the coating vessel and also to alter the characteristics of the medicinal material but by applying a coating containing keratin or gluten in suspension in the presence of graphite and animal charcoal.

The carrier for medicinal substances according to the present invention enables reliable doses of drugs to be administered with exact predetermination of the periods in which the drugs will act upon the organs and in which part of the stomach or intestinal tract the absorption will take place. The invention enables not only particular quantities of the same drug to be absorbed successively or at intervals but also definite quantities of various drugs i.e. the drugs may be alternated as desired.

Having now fully described and ascertained my said invention and the manner in which it is to be performed, I declare that what I claim is:—

1. A process for producing a carrier for medicinal materials characterised in that the materials are reduced to small bodies and the plurality of bodies thus obtained are coated in groups with various coating membranes and the groups thus obtained, each consisting of approximately the same number of bodies, are then mixed together.

2. A process according to Claim 1 characterised in that formed small bodies of medicinal substances are rotated and sprayed with a membranous substance in suspension.

3. A process according to Claims 1 and 2 characterised in that formed small bodies of medicinal substances are rotated and are treated with vaporised membranous material which is deposited on the bodies.

4. A process according to Claims 1 to 3 characterised in that several coatings are produced at least two of which are different from the coating material or the resistance effect.

5. A process according to Claims 1 to 4 characterised in that at least one coating is produced which is insoluble or difficult to dissolve in biological fluids and if necessary is permeable or semi-permeable to such fluids.

6. A process according to Claims 1 to 5 characterised in that at least one coating is produced containing keratin in a form which enables the drugs to be coated in coating vessels without affecting the vessels and consequently also the drugs.

7. A process according to Claims 1 to 6 characterised in that at least one coating is produced containing gluten in a thin form but which is sufficiently resistant to the intestinal juices.

8. A process according to Claims 1 to 7 characterised in that at least one coating is produced containing rubber or a cellulose derivative such as for example a cellulose ester or ether and if necessary softeners such as fat, wax, higher hydrocarbons, and the like may be added.

9. A process according to Claims 1 to 8 characterised in that at least one coating is produced consisting of a fatty material or a higher fixed hydrocarbon which acts as packing.

10. A process according to Claims 1 to 9 characterised in that at least one coating is produced consisting of talcum for the purpose of increasing permeability.

11. A process according to Claims 1 to 10 characterised in that at least one coating is produced containing resins for the purpose of increasing coherence, adherence and hardness.

12. A process according to Claims 1 to 11 characterised in that at least one coating is produced consisting of at least one resin.

13. A process according to Claims 1 to 12 characterised in that at least one coating is produced consisting of keratin, gluten, graphite and animal charcoal as a lacquer.

14. A process according to Claims 1 to 13 characterised in that at least one coating is produced consisting of cocoa butter, stearic acid and solid paraffin.

15. A process according to Claims 1 to 14 characterised in that at least one coating is produced consisting of tolu balsam and collodion.

16. A process according to Claims 1 to 15 characterised in that at least one coating is produced consisting of a mixture of Dammar, Sandarac and mastic resin.

17. A process according to Claims 1 to 16 characterised in that at least one coating is produced which is about 1/100 mm. thick and is capable of resisting biological fluids from 3 to 5 hours.

18. A process according to Claims 1 to 17 characterised in that at least 6 to 10 coatings are produced in which the superimposed layers are not penetrated by the action of the biological fluids before 3 to 5 hours and after bursting of said coatings owing to increase of the internal pressure through osmotic processes the drugs are released.

19. A process according to Claims 1 to 18 characterised in that drug pellets which are particularly insoluble in water or difficult to dissolve therein are coated with a layer of water soluble or water swelling material such as a layer of sugar before the outer coating is applied.

20. A process according to Claims 1 to 19 characterised in that the thickness of the water soluble or water swelling layer applied to the bodies is such that the degree of stability of the body provided with at least one semi-permeable coating against biological fluids is determined thereby.

21. A carrier for medicinal substances according to Claims 1 to 20 consisting of groups of single relatively small bodies containing at least one drug and provided with thin water insoluble but permeable coatings in groups of varying number and resistance against aqueous media.

Dated this 21st day of November, A.D. 1938.

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Patent Attorneys for Applicant.

Witness—J. Spinks.

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